REMARKS/ARGUMENTS

Claims 40-48, 50, 112-119, 121, and 123 are pending in the present application. Claims 40-44, 112, 121, and 123 have been amended without prejudice and without acquiescence. Claims 49, 120 and 122 are canceled herein. Support for claim amendments herein are found in the originally filed claims; support for the term "delivered" in claim 44 is found in original claim 23 and in the specification on Page 71, Lines 15-18. No new matter is entered herein.

The Examiner objects to claim 45 under 37 C.F.R. §1.75(c) as being of improper dependent form for failing to further limit the subject matter of claim 44. Specifically, the Examiner states that the recitation of "nucleic acid" does not further limit the parent claim 44. Applicants respectfully disagree. That is, in claim 45 the term "nucleic acid" is listed as one of several embodiments of the term "delivery vehicle" of claim 44, and it is within the scope of the claims and further limiting that the *atonal* nucleic acid sequence may be in fact administered by a nucleic acid. However, in the interest of furthering the prosecution of this claim, Applicants amend claim 45 herein without prejudice and without acquiescence.

I. Issues Under 35 U.S.C. §112, second paragraph

Claims 40-48, 50, 114, 116 and 117 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to point out and distinctly claim the subject matter of the invention.

Per the Examiner's suggestion regarding this issue, claims 40-44, 112, 121, and 123 are amended herein for further clarification.

The Examiner rejects Claim 114 as indefinite because "a liposome, a protein, a lipid, a carbohydrate" are not vectors. Applicants respectfully disagree. On Page 27, Lines 1-3, Applicants define vector as "a biological vehicle for delivery of a specific entity." Thus, the terms "liposome, protein, lipid and carbohydrate" are well within the scope of the definition. Applicants assert that these embodiments are utilized routinely as vectors in the art. Applicants note that it is well established case law that they may be their own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage. *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947).

The Examiner rejects claims 116 and 117 as indefinite because of the term "operatively linked" as being unclear how to link two coding sequences operatively. Applicants respectfully disagree. One of skill in the art is aware of the meaning of this well-known term. Also, in the specification on Page 72, Lines 5-6, Applicants state that the composition for delivering *Math1* can be a fusion protein, and, specifically in the text immediately preceding, Applicants discuss how the receptor-binding domains of bacterial toxins can be utilized as delivery vehicle. Furthermore, Example 22 describes fusions of an *atonal*-associated nucleic acid sequence with a delivery vehicle sequence, such as Tat, as being operatively linked. Applicants describe an embodiment of this limitation as a fusion protein for subsequent therapeutical purposes. Thus, Applicants assert that a skilled artisan is not only clearly familiar with the term as used in claims 116 and 117 but would understand the term from the context used in the specification.

The Examiner rejects claim 117 as being indefinite because it is allegedly unclear due to the term "protein transduction domain," regarding which part of the protein Applicants are referring to. Applicants respectfully disagree. One of skill in the art is aware of the meaning of this well-known term. In addition, in the specification, on Page 72, Lines 2-6, Applicants state that protein transduction domains can be used for vehicle delivery and provide a well-known example in the art, the HIV Tat protein (Schwarze *et al.*, 1999). Furthermore, Example 22 describes *atonal*-associated nucleic acid sequence in fusions with nucleic acid encoding the exemplary 11 amino acid peptide from HIV. Thus, Applicants assert that the term "protein transduction domain" is clear to one skilled in the art and is furthermore not indefinite.

Issues Under 35 U.S.C. §112, first paragraph

Claims 40-48, 50, 112-119, 121 and 123 are rejected under 35 U.S.C. §112, first paragraph. The Examiner alleges that claims 40-48, 50, 112-119, 121 and 123 contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing. Applicants respectfully disagree.

The Examiner contends that, other than Math1, the specification fails to demonstrate any other *atonal*-associated nucleic acid sequences that share greater than 25% homology

with Math1 and have the same function as Math1. Furthermore, the Examiner states the specification fails to disclose a functional region of Math1 that is responsible for hair cell generation. Bork (2000) is cited by the Examiner regarding unreliability of sequence identity to predict protein function. Thus, the Examiner alleges that "*atonal*-associated nucleic acid" and "nucleic acid encodes a polypeptide which has at least 80% identity to about 20 contiguous amino acid residues of SEQ ID NO:58" is a vast genus, and the structural elements that the nucleic acid must share to have the disclosed hair cell generating function is missing.

Applicants respectfully note that the claimed invention was in fact described in the specification in a way that reasonably conveyed possession was in hand at the time of filing. The claimed invention is written and describes a sufficient amount of embodiments to show possession. For example, a plethora of exemplary *atonal*-associated sequences are provided on Page 28, Line 12 through Page 29, Line 12, derived from a variety of animals. Thus, a skilled artisan would be well taught by the specification, given the many disclosed examples, which *atonal*-associated sequences would be useful and would certainly perceive the Applicants as having possession of this particular element.

The Examiner cites Bork (2000) as stating that sequence identity is insufficient to accurately predict the function of a protein. Applicants have reviewed Bork (2000) and note the reference primarily in context is directed to high-throughput computational analysis, particularly in globally identifying sequences with similar functions. Applicants provide in the instant specification a litany of *specific* sequences that may be used particularly for the explicit purpose of fully describing the invention. Furthermore, although the Examiner states that possession of the invention would not be demonstrated to a skilled artisan because it is not shown that the multitude of *atonal* sequences have the same function, this is irrelevant. Applicant is not required to show each and every embodiment of the claimed invention and the mechanism behind its function. Instead, Applicants are to describe the invention in a way that reasonably conveys to a peer that the invention had been obtained at the date of filing. Thus, Applicants assert that the claims are not limited to a particular domain for the *atonal*-associated nucleic acid sequence. As long as Applicants have described the invention, directed to utilizing an *atonal*-associated sequence, the requirements have been met, and the multitude of *atonal*-associated nucleic acid sequences indicates this has been achieved.

However, in the interest of furthering prosecution of the present case and pursuant to the Written Description Guidelines, Applicants herein amend claims 40, 112 and 121 to contain the element directed toward the nucleic acid sequence encoding a polypeptide having at least about 80% identity to SEQ ID NO:58 and having hair cell generating activity. Based on the present specification and knowledge in the art at the time of filing, Applicants assert that the newly amended claims are directed to subject matter that is certainly both described and enabled at the time of filing.

In light of the above arguments, Applicants kindly request removal of this rejection.

The Action also rejects claims 40-48, 50, 112-119, 121 and 123 as being unpatentable under 35 U.S.C. § 112, first paragraph as containing subject matter that was not described in the specification in such a way as to enable a skilled artisan to make and/or use the invention. According to the Action, undue experimentation would be required to practice the claimed invention, due to the nature of gene therapy and the breadth of the terms "hair cells" and "*atonal*-associated nucleic acid sequence." Applicants respectfully traverse.

Applicants assert that the present claims, in light of the well-detailed specification and the level and knowledge of skill in the art at the time of filing, are presented such that a skilled artisan would be able to make and use the invention. The presently pending claims are directed to methods of generating hair cells for an animal by delivering *atonal*-associated nucleic acid sequence to a cell of the animal, wherein hair cells develop. As described above, Applicants amend the claims to clarify the term "*atonal*-associated nucleic acid sequence." The specification comprehensively describes delivery of nucleic acid sequences both generally (Page 55, Line 6 through Page 58, Line 10) and in exemplary embodiments (Examples 14-17 and 21). The specification also discusses ear hair cells of different variations (Page 1, Line 13; Page 16, Line 1; Page 5, Line 4; Page 6, Line 2; and Page 80, Line 7), including those of the skin (see, for example, expression of Math1/*lacZ* in FIG. 10B).

Furthermore, Applicants assert that the specification reflected the level of skill in the art at the time of filing, particularly given that other skilled artisans have followed similar strategies for generating hair cell development. Namely, Zheng and Gao (2000) reported that administration of Math 1 (in an overexpressed state) results in extra hair cells in postnatal rat cochlear explant cultures, that Math1 is sufficient for the production of hair cells in the ear,

and, furthermore, that immature postnatal mammalian inner ears retain the competence to generate new hair cells. Thus, both the Applicants and a separate party of researchers have shown that Math1 is important for hair cell generation, notably irrespective of the state of Hes1 and Hes5. Applicants assert the Zine *et al.* (2001) reference cited by the Examiner is irrelevant to the patentability of the invention, particularly given that the invention addresses *atonal*-associated nucleic acid sequences and not in some global fashion any sequence that can generate hair cells in the inner ear.

Applicants also note that around the time of filing, data was being generated by other skilled artisans illustrating effective inner ear gene transfer in an accepted mouse model (subsequently reported by Kawamoto *et al.* (2001)). Applicants assert that mice are accepted model systems for gene therapy. In a ***review*** of gene therapy (Kanzaki *et al.*, 2002), particularly a section directed to inner ear gene therapy (p. 163), these same authors refer to other groups that have performed gene therapy in the inner ear, including using vectors that "yield efficient infection and robust gene expression in the inner ear" (p. 163).

Thus, Applicants assert that the instant specification met the burden for enablement under 35 U.S.C. §112, paragraph 1. However, case law supports Applicants arguments concerning the level of description for a skilled artisan to make and use the present invention commensurate with the scope of the claims.

That is, general standard for enablement under §112, first paragraph has been addressed in the case law repeatedly. For example, in *In re Wright*, 999 F.2d 1557, 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993), the court stated that an enabling Specification teaches those skilled in the art how to make and use the claimed invention in its full scope without "undue experimentation." *Wright*, 999 F.2d at 1560. It is well settled patent law that the first paragraph of § 112 requires nothing more than objective enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). This objective enablement may be provided through broad terminology or illustrative examples. *Id.*

Furthermore, in discussing claim breadth, M.P.E.P. § 2164.03 provides that:

> The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required.

M.P.E.P. § 2164.03, 2100-116 (2000). Should the Examiner feel that the present invention is directed to an art where certain results may be associated with a degree of unpredictability, M.P.E.P. § 2164.03 also supports Applicants' position on enablement rather than that advanced in the Action. That is, M.P.E.P. § 2164.03 further provides:

> It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result.

Id. (quoting *In re Dreshfield*, 45 U.S.P.Q. 36 (C.C.P.A. 1940)). Furthermore, it is well known that the level of skill in the art of the present claimed invention is high. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986)

In contrast to the assessment in the Action, the present disclosure completely complies with the requirements of M.P.E.P. § 2164.03 and *In re Dreshfield* by first providing a disclosure regarding a number of species of *atonal*-associated nucleic acid sequences (Page 28, Line 12 through Page 29, Line 12; Page 46, Line 11 through Page 52, Line 23), rather than a single species; and by second providing a detailed description of vectors and their characteristics (Page 39, Line 7 through Page 44, Line 11). To interchange particular elements for different vectors is absolutely rudimentary in the art. Furthermore, Applicants assert that the specification does in fact provide guidance as to gene delivery (Page 55, Line 5 through Page 58, Line 10).

Determination of whether a rejection is appropriate based on the scope of a claim relative to the scope of the enablement depends on two factors: 1) how broad the claim is with respect to the disclosure and 2) if one skilled in the art is enabled to make and use the entire scope of the invention without undue experimentation. M.P.E.P. §§ 2164.08.

Furthermore, it is clear from the foregoing discussion, and from the Specification, that the claims may encompass inoperative embodiments, such as where a particular *atonal*-associated nucleic acid sequence is not effective for the generation of hair cells. This is not prohibited by the statutes. The Federal Circuit has explained that the fact that claims may encompass inoperative embodiments does not necessarily render them non-enabled, or invalid. *Atlas Powder Co. v. E. I. duPont de Nemours & Co.*, 224 U.S.P.Q. 409, 414 (Fed. Cir.

1984). It is not the function of the claims to exclude possible inoperative substances. *Atlas Powder*, 224 U.S.P.Q. at 414.

Section 112 simply requires that there be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill in the relevant art how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Satisfaction of the enablement requirement is not precluded by the necessity of some experimentation. *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984). In *Angstadt*, the predecessor court to the Federal Circuit found that disclosure of many operable embodiments and one inoperative embodiment did not render a claim broader than the enabled scope because determination of the operable embodiments did not involve undue experimentation. *In re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976). Though some testing of constructs containing *atonal*-associated nucleic acid sequence falls within the scope of the claims, one skilled in the art would be directed by disclosures in the Specification and knowledge in the art to identify atonal-associated nucleic acid sequences that would be effective for hair cell generation. With these disclosures, one skilled in the art could determine operable embodiments of the invention without undue experimentation.

Furthermore, Section 112 does not require that the Applicant describe exactly the subject matter claimed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991). Moreover, it is not necessary that a patent Applicant test all the embodiments of his invention. *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991) (citing *In re Angstadt*, 537 F.2d 498, 502, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976)). The patent Applicant simply must provide a disclosure which sufficiently enables one skilled in the art to carry out the invention commensurate with the scope of the claims. *Amgen*, 927 F.2d at 1213.

Applicants submit that satisfaction of the enablement requirement is not precluded by the necessity of some experimentation. *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984). Applicants further submit that the Specification does in fact provide guidance as to gene therapy, particularly in the section of the specification entitled "Gene Therapy Administration" (Page 55, Line 5 through Page 58, Line 10).

> Applicants further assert that it is an established matter of law that the Patent Office has no concern over breadth of term; its only relevant concern should be over truth of such assertion; first paragraph of 35 U.S.C. 112 requires nothing more than objective enablement; how such a teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

As described in the paragraphs above, the claims are enabled by the specification to make and use *atonal*-associated nucleic acid for the generation of hair cells in an animal, and the disclosure teaches this using illustrative examples on Page 95, Line 16 through Page 100, Line 14. Therefore, the requirements of 35 U.S.C. 112 are fulfilled.

Applicant has examined *Ex parte Forman*, and found the standard set for undue experimentation is a subjective one, as described below

> The determination of what constitutes undue experimentation in a given case requires the application of a **standard of reasonableness**, having due regard for the nature of the invention and the state of the art: *Ansul Co. v. Uniroyal, Inc.*, 448 F.2d 872 (2nd Cir. 1971). (Emphasis added)

Applicants point out that whether a **mechanism** by which a chemical or biological process is accomplished is unknown and whether that process **works** are two different questions. The fact that the exact mechanism and/or functional polypeptide domain by which *atonal* is effective for hair cell generation is unknown is irrelevant to the patentability of the claims presented herein. The test for enablement is stated in M.P.E.P. § 2164.01 as:

> whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with the information known in the art without undue experimentation.

United States v. Telectronics, Inc., 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 188 USPQ 659 (CCPA 1976). However, it is submitted that the disclosures in the Specification, as described in the preceding paragraphs, meet the test for objective enablement of the claimed invention. It is further submitted that disclosure of the

exact biological functional domain of action of *atonal*-associated nucleic acid is not necessary for objective enablement.

However, in the interest of furthering prosecution of the present case, Applicants herein amend claims 40, 112 and 121 to contain the element directed toward the nucleic acid sequence encoding a polypeptide having at least about 80% identity to SEQ ID NO:58 and having hair cell generating activity. Based on the present specification and knowledge in the art at the time of filing, Applicants assert that the newly amended claims are directed to subject matter that is certainly both described and enabled at the time of filing.

Attached hereto are both a marked-up version of the changes made to the specification and claims by the current amendment and a copy of all pending claims.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Applicants believe no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P01899US2 from which the undersigned is authorized to draw.

Dated: Sept. 3, 2002

Respectfully submitted,

By Melissa L. Sistrunk

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please replace the second full paragraph on Page 51 (Lines 7-14) with the following paragraph:

It will also be understood that this invention is not limited to the particular nucleic acid or amino acid sequences of SEQ ID NO:2 through SEQ ID NO:66, of which sequences are amino acids. Recombinant vectors and isolated nucleic acid segments can therefore variously include these coding regions themselves, coding regions bearing selected alterations or modifications in the basic coding region, and they can encode larger polypeptides or peptides that nevertheless include such coding regions or can encode biologically functional equivalent proteins, polypeptide or peptides that have variant amino acids sequences.

Please also replace the first full paragraph on Page 28 (Lines 4-11) with the following paragraph (please note the underlined characters in the first sentence are represented identically in the specification; the only material amended is the removal of the hyperlinke in the last sentence):

Examples of *atonal*-associated include but are not limited to *Math1* (mouse *atonal* homolog 1), *Cath1* (chicken *atonal* homolog 1), *Hath1* (human *atonal* homolog 1), and *Xath1* (*Xenopus atonal* homolog 1). Such examples are represented in SEQ ID NO:1 through SEQ ID NO:66, although others very likely exist in related organisms. A skilled artisan is cognizant of means to identify such sequences which have significant similarity, such as searching database collections of nucleic and amino acid sequence located on the World Wide Web [, including http://www.ncbi.nlm.nih.gov/Genbank/GenbankSearch.html.].

In the claims:

40. (Amended Once) A method of generating hair cells for an animal, comprising delivering a therapeutically effective amount of an *atonal*-associated [amino acid sequence or] nucleic acid sequence to a cell of said animal, wherein hair cells develop in said animal and wherein said *atonal*-associated nucleic acid sequence encodes a polypeptide that has hair

cell generating activity and has at least about 80% identity to about 20 contiguous residues of SEQ ID NO:58.

41. (Amended Once) The method of claim 40, wherein said *atonal*-associated [amino acid sequence or] nucleic acid sequence is Math1.

42. (Amended Once) The method of claim 40, wherein said *atonal*-associated amino acid sequence or nucleic acid sequence is Hath1.

43. (Amended Once) The method of claim 40, wherein said delivery comprises injecting into an inner ear a therapeutically effective amount of an *atonal*-associated [amino acid sequence or] nucleic acid sequence.

44. (Amended Once) The method of claim 40, wherein said [amino acid sequence or] nucleic acid sequence is [administered] delivered by a delivery vehicle.

45. (Amended Once) The method of claim 44 wherein said delivery vehicle is selected from the group consisting of an adenoviral vector, a retroviral vector, an adeno-associated viral vector, a plasmid, a liposome, a peptide, [a nucleic acid,] a lipid, a carbohydrate and a combination thereof.

112. (Amended Once) A composition comprising an *atonal*-associated [amino acid sequence or] nucleic acid sequence in combination with a delivery vehicle, wherein said delivery vehicle results in delivery of a therapeutically effective amount of *atonal*-associated nucleic acid sequence [or amino acid sequence] into a cell, and wherein said *atonal*-associated nucleic acid sequence encodes a polypeptide that has hair cell generating activity and has at least about 80% identity to about 20 contiguous residues of SEQ ID NO:58.

121 (Amended Once) A nucleic acid sequence encoding [the fusion protein of claim 120] a fusion protein comprising an *atonal*-associated amino acid sequence or fragment thereof and a desired amino acid sequence, wherein said *atonal*-associated nucleic acid sequence encodes a polypeptide that has hair cell generating activity and has at least about 80% identity to about 20 contiguous residues of SEQ ID NO:58.

123. (Amended Once) The composition of claim 112, wherein the composition further comprises an additional [amino acid sequence or] nucleic acid sequence that is not an *atonal*-associated nucleic acid sequence [or amino acid sequence].